Remarks

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 41-45 are pending in the application, with 41 being the only independent claim.

Support for the amendments to claim 41 is as follows:

The opening clause of Claim 41 has been amended to recite that the "preparation" is a preparation of clostridial toxin derivatives. Support for this amendment can be found in Applicants' specification, for example, on page 4, lines 15-17.

Previous parts (i) and (ii) of Claim 41 have been combined, thus addressing the Examiner's clarity rejections with regard to alleged overlap between these two parts of the claim. Hence, previous part (iii) is now presented as new part (ii).

Part (i) of Claim 41 has been amended to recite that the first ligand does not bind to the clostridial toxin derivatives. Support for this change can be found in Applicants' specification, for example, on page 5, lines 5-7, page 9, lines 30-31, and page 11, lines 18-19. New part (ii) of Claim 41 also recites that the second ligand does not bind to the clostridial toxin derivatives present in the eluate. Support for this change can be found in Applicants' specification, for example, on page 9, lines 12-14.

The expression "ligand-toxin complex" in Claim 41 has been amended for the sake of clarity to recite "first ligand-clostridial toxin complex."

Claim 41 has also been amended to recite that the eluate comprises the clostridial toxin derivatives. Support for this change can be found in Applicants' specification, for example, on page 8, lines 25-29.

The binding activity of the second ligand has been clarified in new part (ii) of Claim 41, and thus recites that the second ligand selectively binds to the first ligand, or selectively binds to the first ligand-clostridial toxin complex, or selectively binds to clostridial toxin, if present in the eluate. Support for this change can be found in Applicants' specification, for example, on page 10, lines 5-6 and 29-30, and Example 3. Specific support for the "if present" wording can be found, for example, in Applicants' specification on page 9, lines 18-21.

Previous part (iv) of Claim 41 has been deleted, and replaced by a final clause that recites "thereby removing clostridial toxin from the preparation of clostridial toxin derivatives". Support for this change can be found in Applicants' specification, for example, on page 9, lines 18-21 of the present specification.

Applicants believe that the above described amendments do not introduce new matter and request that they be entered.

I. New Matter Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner has alleged that the pending claims lack descriptive support in the specification as filed. Office Action, page 4. In more detail, the Examiner has alleged that Example 3 does not provide adequate descriptive support for Claim 41 over its entire scope. In the Examiner's opinion, the specification provides support only for removing BoNT/A from a preparation containing LH_N/A fragments by antibody affinity chromatography. In addition, the Examiner has alleged that the specification provides no descriptive support for the method steps recited in previous part (ii) of Claim 41.

A. "Preparation"

Claim 41 has been amended to recite that the preparation from which the clostridial toxin is removed is "a preparation of clostridial toxin derivatives." Clostridial toxin derivatives are useful as diagnostic tools and/or therapeutics, and it is thus advantageous to minimise the toxicity of these preparations by removing toxins (*i.e.* clostridial holotoxin). *See* page 3, lines 8-11, and page 4, lines 1-23. The presently claimed method is thus adequately supported by the specification as filed and we would ask that the Examiner's rejection be withdrawn.

B. "Clostridial Toxin"

The Examiner is incorrect to take the view that the present specification does not support removing clostridial toxins other than BoNT/A.

As explicitly recited in the specification on page 11, lines 1-4, the present invention is of application to any clostridial toxin, including botulinum and tetanus toxins. Thus, it is evident from the specification that the present invention is not limited to botulinum toxins. Furthermore, 7 botulinum toxins are known, corresponding to serotypes A, B, C1, D, E, F, and G. Thus, it is evident that the specification provides descriptive support for a range of clostridial toxins and is not limited to removal of the specific neurotoxin BoNT/A.

In this regard, a skilled person would recognise that BoNT/A is representative of all clostridial toxins, and that Example 3 is therefore equally applicable to removal of any clostridial toxin from a preparation of clostridial toxin derivatives.

C. ***"First and Second Ligands"***

Contrary to the Examiner's allegation, these terms should not be limited according to the specific molecules used in Example 3 (*i.e.*, an anti-BoNT/A monoclonal antibody and Protein G, respectively).

With regard to the "first ligand," the only requirements of this ligand are that it selectively binds to the clostridial toxin and that it does not bind to the clostridial toxin derivative. *See* page 9, lines 30-31. Thus, any molecule that performs these functions is suitable for use as a first ligand in the present invention. In this regard, the specification provides written basis for a range of ligands other than antibodies. By way of example, page 7, lines 14-18, describes the use of the natural receptor (or a version of the receptor) for which the toxin has an affinity. Furthermore, the first ligand is not even limited to being a protein. As discussed in the paragraph spanning pages 7-8 of the present specification, the first ligand may be a metal ion (such as an immobilised zinc ion) since metal ions selectively bind clostridial toxins -- but not clostridial toxin derivatives, thus enabling removal of clostridial toxin from a preparation of clostridial toxin derivatives.

With regard to the second ligand, the only requirements of this ligand are that it selectively binds to the first ligand, or to the first ligand-clostridial toxin conjugate, or to the clostridial toxin, thereby enabling removal of the clostridial toxin from the preparation; and that it does not bind to the clostridial toxin derivative. Thus, any molecule that performs these functions is suitable for use as a second ligand in the present invention. By way of example (page 10, lines 11-12), the second ligand may be an antibody or immunoglobulin binding domain. The specific molecule Protein G, as exemplified in Example 3, is representative of the wide range of possible protein ligands

that may be used for this step in the purification process. However, in the alternative, a metal ion could be used for the second ligand (see the paragraph spanning pages 7-8 of the present specification).

Thus, the Examiner is incorrect to take the view that the terms "first" and "second" ligand should be limited by reference to specific antibodies, and we would ask that the Examiner's rejections be withdrawn.

D. Method Steps

The Examiner is incorrect to allege that the present specification fails to provide adequate support for forming an immobilised conjugate and an eluate and contacting the eluate with a second ligand.

In this regard, detailed written basis for amended Claim 41 is provided above (*see* section headed "Amendments"). Further basis for the allegedly unsupported method steps is on pages 9-10 of the present specification. Lines 1-2 of page 9 recite the use of two different affinity techniques in combination, and lines 9-14 of page 9 recite the use of the additional step of contacting the toxin derivative preparation (*i.e.*, the eluate) with a second ligand.

The second ligand selectively binds to the first ligand or binds selectively to the ligand-toxin conjugate. *See* lines 4-6 of page 10. Alternatively, it is apparent from lines 29-30 of page 10 that the second ligand may bind to the BoNT toxin *per se*. Toxin, or first ligand-clostridial toxin conjugate, may be present in the eluate if the ligand-toxin conjugate has become detached from the first affinity column and elutes from the column in combination with the toxin derivatives. Use of a second ligand thus enables the

clostridial toxin to be removed from the eluate, and thus from the preparation of clostridial toxin derivatives.

Hence, because claim 41 is supported by the specification, Applicants respectfully request that the Examiner's new matter rejection be withdrawn.

II. Distinctness Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 41-45 under 35 U.S.C. §112, second paragraph, as being indefinite. Office Action, page 5. Applicants respectfully traverse the rejection. However, solely to expedite prosecution, and not in acquiescence to the rejection, Applicants have amended claim 41.

The Examiner's clarity rejection with regard to the expression "substantially free" does not apply to the amended claims, which do not recite this expression.

The Examiner's rejections in part (b) and (c) of this section with regard to the binding step do not apply to amended Claim 41, in which this step is recited just once (new part (i)). Thus, part (i) of amended Claim 41 recites that the first ligand selectively binds to the clostridial toxin, but does not bind to the clostridial toxin derivatives, thereby forming an immobilised first-ligand-clostridial toxin complex and an eluate. This wording - and in particular, the order of the applying, binding and contacting steps of Claim 41 - is thus clear, and we would ask that the Examiner's rejection be withdrawn.

The Examiner's rejection in part (d) of this section with regard to clarity of the eluate does not apply to amended Claim 41. In more detail, part (i) of Claim 41 recites that the eluate may contain an amount of the ligand-toxin complex and recites in new part (ii) that the second ligand selectively binds to the first ligand, or selectively binds to the first ligand-clostridial toxin complex, or selectively binds to clostridial toxin, if

present in the eluate. Thus, there is no inconsistency of wording within Claim 41 as amended and Claim 41 is thus clear. We would therefore ask that the Examiner's rejection be withdrawn.

The Examiner's rejections in parts (e), (f) and (h) of the Official Action do not apply to amended Claim 41, which provides clear antecedent basis for referring to "the first ligand-clostridial toxin complex" and "clostridial toxin."

With regard to the Examiner's rejection in part (g) of this section, the binding activities of the second ligand have been qualified by reference to the first ligand, the clostridial toxin or the first ligand-clostridial toxin complex. Thus, it is clear that the second ligand may selectively bind to any of these molecules, and the Examiner's rejection no longer applies to the pending claims.

In response to the Examiner's allegation that the expression "ligand-toxin complex" lacks clarity (part (i) of this section) we have amended this expression to recite "first ligand clostridial toxin complex," which is clear.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. §112, second paragraph.

Conclusion

All of the stated grounds of rejection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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